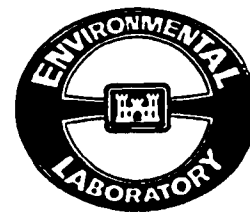


Environmental Effects of Dredging Technical Notes



Dioxin in Sediments: Application of Toxic Equivalents Based on International Toxicity Equivalency Factors to Regulation of Dredged Material

Purpose

This technical note explains the origin and meaning of the dioxin toxic equivalent (TEQ) concept, reviews the application of TEQs to dredged sediment evaluations, examines the underlying assumptions of the application, considers appropriate and inappropriate usage, and discusses a possible alternative to the analytical chemistry-based calculation of TEQs.

Background

A dioxin TEQ expresses the toxicity of a mixture of related compounds in a sample as though the sample contained an equivalent amount of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), thought to be the most toxic environmental contaminant. TEQs have been used in risk assessment in some of the European states for several years.

The method was standardized in 1988 using the International Toxicity Equivalency Factors (I-TEFs) proposed by the NATO Committee on the Challenges of Modern Society (CCMS) Pilot Study on International Information Exchange on Dioxin and Related Compounds (CCMS 1988a,b). The I-TEF method has now been adopted by Canada and the United States, as well as the Netherlands, Great Britain, and the Nordic countries.

Although intended as a procedure for human health risk assessment, TEQs have recently been extended in use to the regulation of open-water disposal of dredged sediments. Some regional offices of the U.S. Environmental Protection Agency (USEPA) and several State resource agencies have either implemented the use of TEQs or propose to require their use in environmental regulation.

In concept, the I-TEF method for calculation of dioxin TEQs can be applied whenever a sample contains measurable amounts of any of the polychlorinated dibenzo-*p*-dioxin (PCDD) or polychlorinated dibenzofuran (PCDF) congeners for which toxic equivalent factors (TEFs) have been assigned. The toxicity of these compounds is thought to be additive, and summation of TEFs is considered to express the potential toxicity of the sample as though it contained an equivalent amount of 2,3,7,8-TCDD.

It is not necessary that 2,3,7,8-TCDD itself be detected in the sample, and polychlorinated biphenyls (PCBs) and other chemicals structurally related to the PCDDs and PCDFs are not included in the I-TEF calculation. The calculation of TEQs using TEFs involves highly expensive trace chemical analysis procedures and has other drawbacks as well as significant strengths.

Additional Information

For additional information, contact the authors, Mr. Victor A. McFarland, (601) 634-3721; Ms. Joan U. Clarke, (601) 634-2954; Dr. Paul W. Ferguson, Northeast Louisiana University, (318) 342-1695; or the manager of the Environmental Effects of Dredging Programs, Dr. Robert M. Engler, (601) 634-3624.

Introduction

Polychlorinated dibenzo-*p*-dioxins, especially 2,3,7,8-TCDD, are among the most toxic and persistent of environmental contaminants. These and the structurally similar PCDFs, the PCBs, and other groups of polyhalogenated aromatic hydrocarbons (PHHs) are associated with genotoxic and cytotoxic effects, as well as body weight loss, reproductive impairment, acute lethality, chloracne, liver damage, edema, and other toxicities (Greig 1979, Kociba and Cabey 1985, Kociba and others 1978, Safe 1987). Much concern has arisen in recent years over the widespread occurrence and potential for toxicity of these chemicals in the aquatic environment, including sediments slated for dredging and disposal.

Most dioxin research to date has focused on 2,3,7,8-TCDD. Nevertheless, there are thousands of other PHH compounds, including 75 PCDD congeners and 135 PCDF congeners, and it is appealing to try to understand the potential toxicity of some of these related compounds in terms of the more familiar (and most toxic) 2,3,7,8-TCDD. Thus, dioxin "toxic equivalents" have been formulated in an attempt to express the combined toxicity of a mixture of PHH in a sample as though the sample contained an equivalent amount of 2,3,7,8-TCDD alone.

The rationale for TEQs is the fact that substances with molecular structures similar to 2,3,7,8-TCDD (that is, those that are isosteric) exhibit the same kind of toxicities, differing mainly in potency of the effect. This phenomenon proceeds from the fact that reversible binding to an intracellular receptor protein, the *Ah* receptor, is the initial event in the series of steps that lead to dioxin-type toxicities. Binding to the *Ah* receptor requires certain molecular structural

characteristics shared by 2,3,7,8-TCDD and its PHH isosteres. A PHH can be assigned a TEF expressing its toxicity as a fraction of 2,3,7,8-TCDD toxicity. The product of the concentration of a PHH compound and its TEF normalizes the toxicity of that compound in a sample to an equivalent amount of 2,3,7,8-TCDD. Summation of the products of TEF and PHH concentrations in a sample yields a TEQ. The TEQ can then be treated as though it were the concentration of 2,3,7,8-TCDD in the sample for purposes of risk assessment.

This technical note describes the use of TEQs in regulatory decision-making processes involving dioxin-containing dredged sediments. Shortcomings in the present use of TEQ methodology are described and supported by examination of recent cases where TEQs have been used in regulatory decisions. An alternative approach based on bioassay-derived TEQs shows promise in overcoming many of the problems associated with TEQs as currently derived from chemical analysis.

TEQs in Aquatic Environmental Assessments

Dioxin TEQs were standardized in 1988 using International Toxicity Equivalency Factors (I-TEFs) (Table 1). The derivation of I-TEFs was based on several criteria; however, a single long-term carcinogenicity study on rats (Kociba and Cabey 1985, Kociba and others 1978) was given the highest priority (CCMS 1988a,b; Kutz and others 1990; Safe 1990). As such, I-TEFs do not reflect the large variability observed when the potency of individual PHHs is compared with the potency of 2,3,7,8-TCDD using specific responses in different organisms. For example, there is a nine hundred-fold difference for one coplanar PCB congener in the TEF calculated for aryl hydrocarbon hydroxylase (AHH) induction in chick embryo and in intact rat (Table 2).

I-TEFs were never developed with ecological protection in mind. Instead, the I-TEFs represent a synthesis reached by a committee of experts using ranked criteria in which potential carcinogenicity in humans was given first priority. All data used in the derivation of I-TEFs were obtained from mammalian (primarily rodent) studies. Thus, if I-TEFs are used to calculate TEQs in evaluations of dioxin-contaminated sediment effects on aquatic biota, there must be an implicit assumption of a parallel between potency for human carcinogenicity and toxic effect in submammalian species.

The research supporting this assumption remains to be done. In the interim, the most appropriate application of I-TEF-based TEQs in environmental assessments is in terms of risk to human consumers of contaminated fish and shellfish. If used in this context, I-TEFs appear to represent the best approximation presently available for the interpretation of analytical chemical data in toxicological terms.

I-TEFs have been agreed upon for 17 PCDD and PCDF congeners containing the chlorine 2,3,7,8-substitution pattern. Not included are the PCBs and other structurally related PHHs. Some of these compounds, particularly the

Table 1. International Toxicity Equivalency Factors

<u>PCDD Congener</u>	<u>I-TEF</u>	<u>PCDF Congener</u>	<u>I-TEF</u>
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	2,3,4,7,8-PeCDF	0.5
		1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,7,8,9-HxCDF	0.1
1,2,3,6,7,8-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
		2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
OCDD	0.001	OCDF	0.001

Table 2. Toxic Equivalent Factors Calculated for 3,3',4,4'-Tetrachlorobiphenyl for Several Responses and Species¹

<u>Response</u>	<u>TEF</u>
Body weight loss (rat)	<0.0001
Thymic atrophy (rat)	<0.0002
Thymic lymphoid development (mouse)	0.00067
AHH induction, in vitro (H4IIE cell line)	0.001 to 0.002
AHH induction, in vivo (rat)	0.00001
AHH induction, in vitro (chick embryo hepatocytes)	0.009
Receptor binding	0.0023

¹ From data presented in Table 15 of Safe (1990).

coplanar PCBs, may pose a greater threat to both wildlife and humans than do the dioxins and furans (Dewailly and others 1991; Niimi and Oliver 1989; Tanabe and others 1987a,b).

Safe (1990) proposed an expansion of the I-TEF list to include coplanar polychlorinated and polybrominated biphenyls, along with brominated and bromo/chloro dibenzo-*p*-dioxins and dibenzofurans. Such an expansion appears appropriate for the coplanar PCBs since these chemicals are abundant and are apparently becoming enriched rather than disappearing from the environment (Tillet and others 1992).

Because I-TEFs are summed to obtain a TEQ, additivity of toxic effect of the individual PCDD and PCDF congeners is assumed, and possible synergism or antagonism is ignored. In fact, antagonistic effects among PHH congeners in a mixture have been demonstrated in a number of cases. The PCB mixture

Aroclor 1254, other Aroclor mixtures, and specific individual PCB, PCDD, and PCDF congeners have all been shown to antagonize the toxic effects of 2,3,7,8-TCDD in mammalian studies (Astroff, Romkes, and Safe 1989; Bannister and others 1987; Davis and Safe 1990; Haake and others 1987; Prokipcak and others 1990; Waern et al. 1989, 1990).

The current method of calculating TEQs from I-TEFs and analytical chemistry thus has several shortcomings that limit the utility of the method for environmental regulatory evaluations, not the least of which is high cost. In fact, the I-TEF method was intended by its developers to be only an interim approach that should be replaced, as soon as practicable, by a more definitive bioassay for the determination of TEQs (Barnes 1991, Kutz and others 1990).

Dredged Sediment Evaluations Using TEQs

I-TEF-based TEQs have recently been required in some environmental assessments. The State of Oregon, for example, has promulgated recommendations on the use of TEQs in environmental regulations (Oregon Department of Environmental Quality 1990). The USEPA has adopted TEQs in risk assessment and in rule making, but has not been consistent in their application. For example, in a recent regulatory decision, Region 10 of the USEPA, in conjunction with the Oregon Department of Environmental Quality, the Washington Department of Ecology, and the Idaho Department of Environmental Quality, set a total maximum daily loading value of 6 mg/day 2,3,7,8-TCDD for the Columbia River Basin based solely on water quality criteria for 2,3,7,8-TCDD, not on TEQs.

On the other hand, several U.S. Army Corps of Engineers (USACE) elements have recently been asked to use TEQs rather than actual concentrations of 2,3,7,8-TCDD in decision making for Federal navigation projects. One such case involved a risk assessment performed by the USACE District, Seattle, in conjunction with maintenance dredging of the Federal Channel at Gray's Harbor, Washington (USACE 1991).

Several tiers of the dredged sediment evaluation tiered testing protocol outlined in the "Green Book" (USEPA/USACE 1991) were performed concurrently to save time. 2,3,7,8-TCDD was detected in only 3 of 17 sediments, at concentrations ranging from 1.5 to 3.9 parts per trillion (ppt). 2,3,7,8-substituted PCDDs were present in some sediment samples, but at such low concentrations that there was no "reason to believe," in a Tier II evaluation of the sediments, that dioxin would be bioaccumulated to detectable levels. All sediment toxicity tests were negative and bioaccumulation tests were inconclusive; thus, there were no Tier III exceedances.

Nevertheless, the District was compelled by the USEPA and state agencies to perform a TEQ-based human health risk analysis on the project sediments. The risk analysis was performed with data generated by assuming concentrations to be equal to one half the detection limit since most samples contained

no detectable dioxins or furans. The outcome of the risk assessment was no incremental human health risk attributable to these compounds.

In another case, the USACE District, Walla Walla, was delayed in 1991 from performing a previously approved maintenance dredging project in the upper Snake River when the "104 Mill Survey" identified a nearby industrial source of dioxin. This delay was resolved by an agreement between the District and USEPA Region 10 to sample the sediments slated for dredging for selected dioxin and furan congeners.

Because the cost of dioxin determinations is so high, the District proposed a plan whereby dioxin would be analyzed only in sediments with the highest total organic carbon (TOC) content (those in which dioxin could be expected to be found, if present). Sediments were collected throughout the project area, and TOC was determined in all samples. The sediment samples were archived until initial dioxin testing of the highest TOC samples was complete. If dioxins were found in the high-TOC samples, the next highest TOC samples would then be analyzed. The analytical results would be used to calculate TEQs.

In a third case involving TEQs, the National Oceanographic and Atmospheric Administration Natural Resources Trustees recently presented the USACE District, Charleston, with concerns regarding dioxin contamination in Winyah Bay, South Carolina. As a result of the "104 Mill Survey," the South Carolina Department of Health and Environmental Control (SCDHEC) sampled organisms and sediments throughout Winyah Bay. They found a few organisms with elevated levels of dioxin TEQs, and 5 of 11 sediment samples had dioxin TEQ levels above 2 pptr.

In January and February 1989, 22 stations were sampled for organisms. Of these samples, 14 exceeded 1 pptr TEQ, and 3 had TEQs exceeding the 25-pptr U.S. Food and Drug Administration (FDA) limit for 2,3,7,8-TCDD in edible fish portions. In August and September 1989, SCDHEC sampled 51 organisms for dioxins. Of these, 24 had TEQs exceeding the 1-pptr detection limit routinely obtained for dioxin in tissue samples, and one exceeded the 25-pptr FDA limit (unpublished data, SCDHEC). Congeners analyzed in the tissue samples were the 17 I-TEFs listed in Table 1; of these, the most frequently occurring were 2,3,7,8-TCDD, OCDD, and 2,3,7,8-TCDF. The Charleston District is evaluating Federal project sediments for three reaches of Winyah Bay using guidance published in the "Green Book" (USEPA/USACE 1991).

Regulatory evaluations of dioxin-containing sediments in the New York-New Jersey Harbor area have been based on the bioaccumulation of 2,3,7,8-TCDD, rather than on TEQs. Bioaccumulation testing using the polychaete *Nereis virens* is performed if dredging project sediments exceed 1 pptr 2,3,7,8-TCDD.

In 1992, the USACE District, New York, proposed guidelines for evaluating dioxin bioaccumulation data (personal communication, John Tavolaro, New York District). If bioaccumulation levels in worms exposed to the dredged sediment were significantly greater (95 percent confidence level) than

bioaccumulation levels in worms exposed to reference sediment, the restrictions described below would apply.

For bioaccumulation of at least 1 pptr 2,3,7,8-TCDD and less than 10 pptr in worms exposed to the dredged sediment, ocean disposal would be allowed and expeditious capping would be required (within 2 weeks, 2 to 1 ratio of cap to capped material). For bioaccumulation of at least 10 pptr and less than 25 pptr, expeditious capping would be required (within 10 days, at least 2 to 1 ratio of cap to capped material), and special measures (such as onboard inspectors) would be taken to ensure that the material was accurately placed and capped. For bioaccumulation of 25 pptr and above, ocean disposal would not be allowed. These protocols have been accepted by the USEPA Region 2 and are to be reassessed within 18 months after completion of the first dredging project involving dioxin evaluation.

As the above examples demonstrate, the regulation of dioxin-containing sediments is far from standardized on a national basis. More research into the relationship between sediment levels and toxicity is certainly required.

Strengths and Weaknesses of I-TEF-based TEQs

Dioxin TEQs are beginning to play a role in environmental evaluations, including regulatory decision making with regard to dredged sediments. Although the calculation of TEQs has been standardized using I-TEFs, their application by state and federal regulatory agencies is by no means consistent. The strengths and weaknesses of I-TEF-based TEQs in environmental evaluations can be summarized as shown below.

Strengths

- Able to recognize the contribution to toxicity of compounds other than 2,3,7,8-TCDD.
- Express the toxic potential of a sample in terms of a single numerical value.
- Provide a means of relating chemical analytical data to biological effect.
- Limits of detection are those of the chemical analysis, presently on the order of 100 to 200 parts per quadrillion for individual congeners.
- When applied to sediment analyses, can be used to determine the necessity for Tier III or Tier IV biological testing.

Weaknesses

- Restricted to PCDDs and PCDFs; not included are PCBs or other structurally related PHHs, some of which are much more abundant in the environment and thus may have greater toxic potential than the dioxins and furans.
- Necessitate highly expensive trace chemical analysis.

- Account for only additivity of toxic effect of the congeners in a mixture, whereas antagonistic effects have also been demonstrated.
- Do not account for the large (several orders of magnitude) species- and response-dependent variability in empirical toxic equivalent factors.
- Are biased toward human health protection and may not accurately assess the real toxicity of dredged material to aquatic biota.
- When applied to sediment data alone, do not address bioavailability, that is, the dose actually delivered to the animal.

Biological Alternatives

TEQs provide a way to express the toxicity of complex mixtures of environmental contaminants that is highly appealing for its simplicity. Basing TEQs on an integrative bioassay rather than on trace chemical analysis would overcome most of the weaknesses mentioned above while retaining most of the strengths, including the simplicity of a single 2,3,7,8-TCDD-equivalent number. One such bioassay is the H4IIE in vitro bioassay, which uses the rat hepatoma H4IIE cell line (Bradlaw and Casterline 1979). This bioassay integrates the additive and antagonistic effects of a mixture into a numerical result (the TEQ) at a cost per sample of 10 to 20 times less than trace chemical analysis.

The H4IIE assay makes use of the fact that toxic potency of dioxin-like compounds correlates strongly with the potency of these compounds to cause induction of certain xenobiotic-metabolizing enzymes. Two of these marker enzymes, ethoxyresorufin-O-deethylase (EROD) and AHH can be measured using highly sensitive fluorescence spectrophotometry, approaching the resolution of gas chromatography/electron capture detection (GC/ECD) at much lower cost. The potency of a mixture of dioxin-like compounds can be compared with the potency of a pure 2,3,7,8-TCDD standard for the induction of AHH and/or EROD using the H4IIE cell line, and the result can be expressed as a TEQ.

The H4IIE cell line has been used to measure TEQs in fish extracts (Casterline and others 1983; Zacharewski, Safe, and Safe 1989) and in the eggs of fish-eating waterbirds (Tillet, Ankley, and Geisy 1989; Tillet and others 1991, 1992). Recently, the procedure was applied to sediments (personal communication, John P. Geisy, Michigan State University) and is now being investigated by the U.S. Army Engineer Waterways Experiment Station as a new procedure for dredged sediment evaluation.

The H4IIE cell line has been used since 1961 (Casterline and others 1983); however, it has only recently begun to find its way into widespread environmental applications and may soon be eclipsed by simpler and more sensitive procedures. Recently, recombinant methods were used to insert dioxin-responsive segments of human genes into a plasmid containing the firefly luciferase gene. In the presence of dioxin or related compounds, the gene responds by expressing luciferase, which can be measured quantitatively with a luminometer (Postlind and others 1992). The method is similar to the H4IIE assay, but is simpler and may prove to be even more sensitive. It appears likely that

advances, such as this, in molecular biology will result in the development of more specific, sensitive, rapid, and less expensive alternatives to analytical chemistry for measuring TEQs.

Conclusions

Use of the I-TEFs to calculate a dioxin TEQ in an environmental sample is an attractive and simple means of relating chemical concentration data to the potential for a toxic effect. Although developed for use in human risk assessment, the concept and practice have been extended to ecological evaluations, including evaluations of dredged sediments intended for open-water disposal. Despite numerous limitations when applied to ecological evaluations of contaminants in dredged sediments, the use of I-TEF-based TEQs provides a means of obtaining toxicologically relevant information from sediment chemistry. Biological methods now under development have the potential of reducing or eliminating many of the problems inherent in the use of I-TEFs.

References

- Astroff, B., Romkes, M., and Safe, S. 1989. "Mechanism of Action of 2,3,7,8-TCDD and 1,3,8-Trichlorodibenzofuran (MCDF) as Antiestrogens in the Female Rat," *Chemosphere*, Vol 19, pp 785-788.
- Bannister, R., Davis, D., Zacharewski, T., Tizard, I., and Safe, S. 1987. "Aroclor 1254 as a 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Antagonist: Effects on Enzyme Induction and Immunotoxicity," *Toxicology*, Vol 46, pp 29-42.
- Barnes, D. G. 1991. "Toxicity Equivalents and EPA's Risk Assessment of 2,3,7,8-TCDD," *The Science of the Total Environment*, Vol 104, pp 73-86.
- Bradlaw, J. A., and Casterline, J. L., Jr. 1979. "Induction of Enzyme Activity in Cell Culture: A Rapid Screen for Detection of Planar Polychlorinated Organic Compounds," *Journal, Association of Official Analytical Chemists*, Vol 62, pp 904-916.
- Casterline, J. L., Jr., Bradlaw, J. A., Puma, B. J., and Ku, Y. 1983. "Screening of Freshwater Fish Extracts for Enzyme-inducing Substances by an Aryl Hydrocarbon Hydroxylase Induction Bioassay Technique." *Journal, Association of Official Analytical Chemists*, Vol 66, pp 1136-1139.
- Committee on the Challenges of Modern Society. 1988a. "International Toxicity Equivalency Factor (I-TEF) Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds," Pilot Study on International Information Exchange on Dioxins and Related Compounds, Report No. 176, North Atlantic Treaty Organization.
- _____. 1988b. "Scientific Basis for the International Toxicity Equivalency Factor (I-TEF) Method of Risk Assessment for Complex Mixtures,"

Pilot Study on International Information Exchange on Dioxins and Related Compounds, Report No. 178, North Atlantic Treaty Organization.

Davis, D., and Safe, S. 1990. "Interactions of 2,3,7,8-TCDD and PCB Mixtures/Congeners: Immunotoxicity Studies," *Chemosphere*, Vol 20, pp 1141-1146.

Dewailly, É., Weber, J.-P., Gingras, S., and Laliberté, C. 1991. "Coplanar PCBs in Human Milk in the Province of Québec, Canada: Are They More Toxic Than Dioxin for Breast Fed Infants?" *Bulletin of Environmental Contamination and Toxicology*, Vol 47, pp 491-498.

Greig, J. B. 1979. "The Toxicology of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Its Structural Analogues," *Annals of Occupational Hygiene*, Vol 22, pp 411-420.

Haake, J. M., Safe, S., Mayura, K., and Phillips, T. D. 1987. "Aroclor 1254 as an Antagonist for the Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin," *Toxicology Letters*, Vol 38, pp 299-306.

Kociba, R. J., and Cabey, O. 1985. "Comparative Toxicity and Biologic Activity of Chlorinated Dibenzo-*p*-dioxins and Furans Relative to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)," *Chemosphere*, Vol 14, pp 649-665.

Kociba, R. J., Keyes, D. G., Beyer, J. E., Carreon, R. M., Wade, C. E., Dittenber, D. A., Kalnins, R. P., Frauson, L. E., Parks, C. N., Barnard, S. D., Hummel, R. A., and Humiston, C. G. 1978. "Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rats," *Toxicology and Applied Pharmacology*, Vol 46, pp 279-303.

Kutz, F. W., Barnes, D. G., Bottimore, D. P., Greim, H., and Bretthauer, E. W. 1990. "The International Toxicity Equivalency Factor (I-TEF) Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds," *Chemosphere*, Vol 20, Nos. 7-9, pp 751-757.

Niimi, A. J., and Oliver, B. G. 1989. "Assessment of Relative Toxicity of Chlorinated Dibenzo-*p*-dioxins, Dibenzofurans, and Biphenyls in Lake Ontario Salmonids to Mammalian Systems Using Toxic Equivalent Factors (TEF)," *Chemosphere*, Vol 18, Nos. 7-8, pp 1413-1423.

Oregon Department of Environmental Quality. 1990. "Water Quality Standards Issue Paper No. 8," Portland, OR.

Postlind, H., Vu, T. P., Tukey, R. H., and Quattrochi, L. C. 1992. "Differential Response of Human *Cyp1*-luciferase Plasmids to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Polycyclic Aromatic Hydrocarbons," *Toxicology and Applied Pharmacology* (in press).

Prokipcak, R. D., Golas, C. L., Manchester, D. K., Okey, A. B., Safe, S., and Fujita, T. 1990. "7-Substituted-2,3-dichlorodibenzo-*p*-dioxins as Competitive Ligands for the Ah Receptor: Quantitative Structure-Activity Relationships (QSARs) and a

Comparison of Human Receptor with Ah Receptor from Rodents," *Chemosphere*, Vol 20, pp 1221-1228.

Safe, S. 1987. "Determination of 2,3,7,8-TCDD Toxic Equivalent Factors (TEFs): Support for the Use of the *in vitro* AHH Induction Assay," *Chemosphere*, Vol 16, pp 791-802.

_____. 1990. "Polychlorinated Biphenyls (PCBs), Dibenzo-*p*-dioxins (PCDDs), Dibenzofurans (PCDFs), and Related Compounds: Environmental and Mechanistic Considerations Which Support the Development of Toxic Equivalency Factors (TEFs)," *CRC Critical Reviews in Toxicology*, Vol 21, pp 51-88.

Tanabe, S., Kannan, N., Subramanian, A., Watanabe, S., and Tatsukawa, R. 1987a. "Highly Toxic Coplanar PCBs: Occurrence, Source, Persistency and Toxic Implications to Wildlife and Humans," *Environmental Pollution*, Vol 47, pp 147-163.

Tanabe, S., Kannan, N., Subramanian, A., Watanabe, S., Ono, M., and Tatsukawa, R. 1987b. "Occurrence and Distribution of Toxic Coplanar PCBs in Biota," *Chemosphere*, Vol 16, Nos. 8-9, pp 1965-1970.

Tillet, D. E., Ankley, G. T., and Geisy, J. P. 1989. "Planar Chlorinated Hydrocarbons (PCHs) in Colonial Fish-Eating Waterbird Eggs from the Great Lakes," *Marine Environmental Research*, Vol 28, pp 505-508.

Tillet, D. E., Ankley, G. T., Verbrugge, D. A., Geisy, J. P., Ludwig, J. P., and Kubiak, T. J. 1991. "H4IIE Rat Hepatoma Cell Bioassay-Derived 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Equivalents in Colonial Fish-Eating Waterbird Eggs from the Great Lakes," *Archives of Environmental Contamination and Toxicology*, Vol 21, pp 91-101.

Tillet, D. E., Ankley, G. T., Giesy, J. P., Ludwig, J. P., Kurita-Matsuba, H., Weseloh, D. V., Ross, P. S., Bishop, C. A., Sileo, L., Larson J., and Kubiak, T. J. 1992. "Polychlorinated Biphenyl Residues and Egg Mortality in Double-Crested Cormorants from the Great Lakes," *Environmental Toxicology and Chemistry*, Vol 11, pp 1281-1288.

U.S. Army Corps of Engineers. 1991. "Human Health Risk Assessment of Seafood Consumption Related to Disposal of Federal Channel Maintenance Dredged Material at South Jetty/Point Chehalais, Gray's Harbor, Washington," USACE District, Seattle, WA.

U.S. Environmental Protection Agency/U.S. Army Corps of Engineers. 1991. "Evaluation of Dredged Material Proposed for Ocean Disposal (Testing Manual)," EPA-503/8-91/001, USEPA Office of Marine and Estuarine Protection, Washington, DC.

Waern, F., Hanberg, A., Manzoor, E., and Ahlborg, U. G. 1990. "TCDD and 2,3,4,7,8-PeCDF Temporal Interaction of Vitamin A Depletion and Hepatic Enzyme-Induction in the Rat," *Chemosphere*, Vol 20, pp 1155-1160.

Waern, F., Hanberg, A., Manzoor, E., Safe, S., and Ahlborg, U. G. 1989. "Interaction of 6-Methyl-1,2,8-trichlorodibenzofuran with TCDD-Induced Vitamin A Reduction," *Chemosphere*, Vol 19, pp 1005-1008.

Zacharewski, T., Safe, L., and Safe, S. 1989. "Comparative Analysis of Polychlorinated Dibenzo-*p*-dioxin and Dibenzofuran Congeners in Great Lakes Fish Extracts by Gas Chromatography-Mass Spectrometry and in vitro Enzyme Induction Activities," *Environmental Science and Technology*, Vol 23, pp 730-735.